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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/068,725	KINDSVOGEL, WAYNE	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/27/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *11-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-10 in the reply filed on 9/27/2004 is acknowledged.

2. Claims 11-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

3. Claims 1-10 are under examination.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 9-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-10 are indefinite for reciting "further comprising administering a composition that comprises an antibody component..." in claim 9. It is unclear if the antibody component recited in claims 9 and 10 is in addition to the antibody component of claim 1 or is the antibody component that binds amino acids 105-166 or 110-118 of SEQ ID NO:4 the same as the antibody component of claim 1, which binds BCMA and TACI?

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the proliferation of B cell tumor cells, comprising administering to the tumor cells or to a subject having B cell tumor cells expressing BCMA and TACI a composition comprising an antibody component that binds both BCMA and TACI and further comprises administering an antibody component that binds to an epitope within a polypeptide consisting of amino acid residues 105-166 or residues 110-118 of SEQ ID NO:4, does not reasonably provide enablement for a method for inhibiting the proliferation of non-B cell tumors comprising administering to the tumor cells or to a subject having tumor cells an antibody component that binds both BCMA and TACI and further comprises administering an antibody component that binds to an epitope within a polypeptide consisting of amino acid residues 105-166 or residues 110-118 of SEQ ID NO:4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They

include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method for inhibiting the proliferation of tumor cells comprising administering an antibody component that binds both BCMA and TACI and further comprises administering an antibody component that binds an epitope within a polypeptide consisting of amino acid residues 105-166 or 110-118 of SEQ ID NO:4. The claims are broad because they do not require that the tumor cells express both BCMA and TACI and thus, encompass a method of inhibiting tumor proliferation with an antibody that binds both BCMA and TACI, wherein the antibody does not bind the tumor cells. The specification teaches antibody treatment of tumor cells expressing both BCMA and TACI (i.e., lymphoma and multiple myeloma) with an antibody that binds both BCMA and TACI (see Examples 1 and 2). The specification does not teach a method of inhibiting the proliferation of just any tumor cells, including tumor cells that do not necessarily express BCMA and TACI, with an antibody that binds both BCMA and TACI. The specification does not enable a method of inhibiting the proliferation of just any tumor cells either in vitro or in vivo with an antibody that binds both BCMA and TACI commensurate in scope with the claims.

The art indicates that B-lymphocyte stimulator (BLyS), also called B cell-activating factor (BAFF), tumor necrosis factor (TNF) homologue that activates

apoptosis, nuclear factor kB (NF-kB, and c-Jun NH_2-terminal kinase (THANK), TNF and apoptosis ligand-related leukocyte-expressed ligand 1 (TALL-1), or zTNF4, is a TNF family member critical for maintenance for normal B-cell development and homeostasis (see Novak et al., Blood, 103(2):689-694, 2004, page 689 left column). Novak et al teach that BCMA is predominantly expressed on B lymphocytes and TACI is expressed on B lymphocytes and activated T cells (see page 689, right column). The ligand zTNF4 (BLyS, BAFF, TALL-1, THANK) binds both BCMA and TACI cell surface receptors and FITC-tagged, soluble zNTF4 specifically binds to various B cell lymphoma cell lines whereas no binding was detected with HL-60 (a promyelocytic cell line) or monocytes, dendritic cells, and purified T cells (see page 53; Gross et al WO 00/40716, 7/13/2002). Gross et al conclude that the specificity for B cells by the ligand zNTF4 and its receptors (BCMA and TACI) suggest that they are useful for the study and treatment of B cell cancers (see page 53).

No guidance or direction is provided to assist one skilled in the art in the use of an antibody that binds both BCMA and TACI for inhibiting the proliferation of just any tumor cells, particularly tumor cells which do not express the cell-surface receptors BCMA and TACI (i.e., non-B cell tumors), nor is there evidence provided that administering an antibody that binds both BCMA and TACI would be therapeutically effective against tumor cells that do not express BCMA or TACI. It appears that undue experimentation would be required of one skilled in the art to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed

methods and absent a working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting the proliferation of just any tumor cells commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1 and 3-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Theill et al (U.S. Patent 6,774,106 B2, priority to 5/12/2000).

The claims are drawn to a method for inhibiting the proliferation of tumor cells in a subject comprising administering an antibody component the binds both BCMA and TACI, wherein the antibody component is a naked BCMA-TACI antibody or naked BCMA-TACI antibody fragment and wherein the BCMA-TACIO antibody is conjugated to a therapeutic agent (i.e., immunoconjugate) selected from a chemotherapeutic drug, cytotoxin, immunomodulator, chelator, boron compound, photoactive agent, photoactive dye and radioisotope.

Theill et al teach a method of inhibiting tumor proliferation in a mammal (i.e., in a subject) comprising administering an antibody (i.e., therapeutic agent) that binds BCMA

and TACI, which are cell-surface receptors that bind APRIL and inhibition of APRIL binding to BCMA and TACI inhibits lymphoma cell growth (see column 11, line 54 to column 12, line 4 and line 67 and columns 13-18). Theill et al teach that the antibody which binds BCMA and TACI is administered with physiologically acceptable salts (i.e., pharmaceutical composition) is a naked antibody or naked antibody fragment (i.e., not conjugated with a therapeutic agent) (see column 11, lines 14-37 and columns). Theill et al teach antibodies comprising a cytotoxic protein (i.e., immunoconjugate) such as plant and bacterial toxins (see column 16, lines 20-23). Thus, Theill et al anticipate the claims.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Theill et al (U.S. Patent 6,774,106 B2, priority to 5/12/2000) in view of Gross et al (WO 00/40716, published 7/13/2000).

Claims 1 and 3-8 have been described supra.

Claim 2 is drawn to inhibiting the proliferation of tumor cells comprising administering to cells cultured in vitro an antibody component that binds both BCMA and TACI.

Theill et al have been described supra. Theill et al do not specifically teach administration of an antibody that binds both BCMA and TACI to tumor cells cultured in vitro or therapeutic agents selected from a chemotherapeutic drug, immnuomodulator, chelator, boron compound, photoactive agent or dye and radioisotope. These deficiencies are made up for in the teachings of Gross et al.

Gross et al teach the TNF ligand, ztnf4 (neutrokine alpha, Blys, BAFF, TALL-1 or THANK), which binds the cell surface receptors BCMA and TACI on B cells resulting in B cell proliferation (see pages 5-6 and 53). Gross et al teach that ztnf4 binds various B cell tumors such as B cell lymphoma cells (i.e., Raji, Burkitt's human lymphoma) and methods for inhibiting the ztnf4-receptor (i.e., ztnf4-BCMA and ztnf4-TACI) interaction with an antagonist for treating multiple myelomas and lymphomas and modifying the proliferation and development of target cells in vitro and in vivo, wherein the antagonist is an antibody that binds TACI or BCMA (see pages 53-59 and Example 18 at page 116). Gross et al also teach antibodies conjugated to drugs, toxins, radionuclides,

cofactors, inhibitors, fluorescent markers, chemiluminescent markers and magnetic particles (see pages 71-74).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for inhibiting the proliferation of B cell tumors in vivo or in vitro comprising administering an antibody that binds both BCMA and TACI for therapeutic benefit of B cell tumors.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for inhibiting the proliferation of B cell tumors in vivo or in vitro comprising administering an antibody that binds both BCMA and TACI for therapeutic benefit of B cell tumors in view of Theill et al and Gross et al because Theill et al teach a method of inhibiting tumor proliferation in a mammal comprising administering an antibody that binds BCMA and TACI and the antibody in conjugated to a cytotoxic polypeptide and Gross et al teach methods for inhibiting the ztnf4-receptor (i.e., ztnf4-BCMA and ztnf4-TACI) interaction with an antibody for treating multiple myelomas and lymphomas and modifying the proliferation and development of target cells in vitro and in vivo. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inhibit both BCMA and TACI receptor function of tumor cells cultured in vitro or in a subject to inhibit tumor cell proliferation for therapeutic benefit of B cell tumors. Further, it would have been obvious to one of ordinary skill in the art to optimize the tumor cell treatment in cells cultured in vitro prior to proceeding to an animal model and ultimately to clinical trials for human therapy. Thus, it would have been obvious to one skilled in the art to

have produced a method for inhibiting the proliferation of B cell tumors in vivo or in vitro comprising administering an antibody that binds both BCMA and TACI for therapeutic benefit of B cell tumors in view of Theill et al and Gross et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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LARRY R. HELMS, PH.D
PRIMARY EXAMINER